

## **PCT**

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference  Ladner 7C-P	FOR FURTHER ACTION	See Notification of Transmittal of Inter- Preliminary Examination Report (Form PCT/IP					
International application No. PCT/US92/01501	International filing date (day/n 28.02.92	month/year) Priority date (day/month/year) 01.03.91					
International Patent Classification (IPC) C12N15/15	or national classification and I	IPC .					
Applicant Protein Engineering Corporation et al							
<ol> <li>This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</li> <li>This REPORT consists of a total of sheets.</li> <li>This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings amended during international preliminary examination and/or containing rectifications made before this Authority.</li> <li>These annexes consist of a total of sheets.</li> </ol>							
3. This report contains indications and corresponding pages relating to the following items:  I Basis of the report  II Priority  III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability  IV Lack of unity of invention  V Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement  VI Certain documents cited  VII Certain defects in the international application  VIII Certain observations on the international application							
Date of submission of the demand	Date	e of completion of this report					
24.09.92		<b>2 1</b> . 06, 93					
Name and mailing address of the IPEA/ European Patent Office, Erhardtst W-8000 Munich 2 Tel. (+49-89) 2399-0, Tx: 523656 Fax: (+49-89) 2399-4465	trasse 27	J. Espen					

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US 92/01501

I. Basis of the report							
1. This report has been drawn up on the basis of:							
χ the international application as originally filed.							
the description	, pages	, as originally filed,					
	pages	, filed with the demand,					
	pages	, filed with the letter of,					
	pages	, filed with the letter of,					
the claims,	No	, as originally filed,					
	No	, as amended under Article 19,					
	No	, filed with the demand,					
	No	, filed with the letter of ,					
	No	, filed with the letter of,					
the drawings,	sheets/fig.	, as originally filed,					
	sheets/fig.	, filed with the demand,					
		, filed with the letter of,					
	sheets/fig.	, filed with the letter of,					
	losure as filed, as indicated	sheets of drawings/figures No.:					
II. Priority							
1. This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:							
copy of the earl	ier application whose priori	ty has been claimed.					
translation of th	e earlier application whose	priority has been claimed.					
2. This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.							
Thus for the purposes of this re	port, the international filing	date indicated above is considered to be the relevant date.					



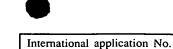
International application No.

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V.	Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement			
1.	STATEMENT			
	Novelty (N)	Claims Claims	01 - 13	YES NO
	Inventive Step (IS)	Claims Claims	01 - 13	_ YES _ NO
	Industrial Applicability (IA)	Claims Claims	01 - 13	_ YES _ NO
2.	CITATIONS AND EXPLANATIONS			

Please, see separate sheet.





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## VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

The International Preliminary Examining Authority has to issue a warning concerning a lack of unity of the present International Application (Rule 13, PCT).

The present application may be subdivided in the following groups of inventions:

- 1) inhibitors of human neutrophil elastase derived from BPTI or ITI D1 (Claims 1 and 3, respectively).
- 2) inhibitors of human cathepsin G derived from BPTI (Claim 2).
- 3) inhibitors of human neutrophil elastase consisting of derivatized peptides (Claims 7 11).

Form PCT/IPEA/409 (sixth sheet) (July 1992)





## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

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VIII. Certain observations on the international applic	atio
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The following observations on the claims of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The claims should be clear by themselves. However, Claims 1-2 contain internal denominations (EPi N..., Epi C...) meaningless for the person skilled in the art.



1). The present International Application relates to muteins of bovine pancreatic trypsin inhibitor (BPTI), inter-alpha-trypsinininhibitor-D1 (ITI-D1) and other Kunitz domain-type inhibitors which have a high affinity for elastase and cathepsin G.

Furthermore, the present application also relates to derivatized peptides which bind elastase or cathepsin G, and more particularly to elastase-binding polypeptide (EpiNe) type human neutrophil elastase (hNE) inhibitors.

Said inhibitors may be grouped into Class I, II, and III

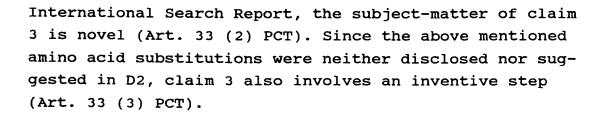
2). The subject-matter of claim 1 relates to BPTI muteins having amino acid substitutions around the P1 region. With respect to claim 1, the closest prior art document is EP-A-0 307 592 (D1) which discloses BPTI variants. Since the specific amino acid combinations of the EpiNe... claimed in claim 1 and shown in Tables 207-208 of the present application are neither described nor suggested in D1, the subject-matter of claim 1 is novel (Art. 33 (2) PCT) and also involves an inventive step (Art. 33 (3) PCT).

inhibitors (Fig. 8, 9, and 12 respectively).

The above comment also applies to claim 2, the subject-matter of which are inhibitors of human cathepsin G having amino acid (a.a.) substitutions around the P1 region (a.a. 15-19 and a.a. 39-42) of BPTI.

Claim 3 refers to inter-alpha-trypsinhibitor (ITI-D1) muteins. With respect to claim 3, the closest prior art document is EP-A-0 041 508 (D2).

Claim 3 differs from D2 in that amino acid substitutions in ITI (numbering according to D2) are disclosed for example in positions 22, 23, 25, 37, 39, and 40. Having regard to the documents cited in the



Claims 7-12 relate to derivatized peptides which are inhibitors of human neutrophil elastase.

With respect to said claims the closest prior art document is  $EP_7A-0$  195 212 (D3).

It appears that D3 neither discloses nor suggests the subject-matter of said claims, and, therefore, said claims seem to meet the requirements of Art. 33 (2) and (3) EPC.

The industrial applicability of claims 1-13 is acknowledged (Art. 33 (4) PCT).